Journal of Forensic and Legal Medicine 26 (2014) 5–9

Contents lists available at ScienceDirect

Journal of Forensic and Legal Medicine

journal homepage: www.elsevier.com/locate/jflm

Case report

# Sudden death of a 15-year-old girl due to fulminant type 1 diabetes mellitus—Diabetic ketoacidosis induced cerebral edema?

Hongmei Dong*, Liang Liu, Yiwu Zhou, Jiao Mu, Ji Zhang

*Department of Forensic Medicine, Tongji Medical College of Huazhong University of Science and Technology, 13 Hangkong Road, Wuhan, Hubei 430030, People's Republic of China*

ARTICLE INFO

*Article history:*
Available online 16 May 2014

*Keywords:*
Fulminant type 1 diabetes mellitus
Unexpected death
Cerebral edema
Diabetic ketoacidosis

ABSTRACT

Sudden death from fulminant type 1 diabetes mellitus is uncommon in forensic practice. Here we report the sudden death of a 15-year-old girl who presented with vomiting, fever and abdominal pain and died unexpectedly. Postmortem examination showed severe pancreatic islet destruction, cerebral edema and lipid vacuolization of the epithelium of the renal proximal tubules and liver cells. The biochemical analysis in reserved heart blood and vitreous fluid indicated the elevated levels of glucose and ketone bodies and lower glycosylated hemoglobin and C-peptide. The cause of death was attributed to fulminant type 1 diabetes mellitus which led to diabetic ketoacidosis-associated cerebral edema. This report suggested that the histological examination of the pancreas, liver and kidney, insulin immunohistochemistry, as well as biochemical analysis could be useful for the diagnosis of diabetes related death.



## 1. Introduction

Type 1 diabetes, previously called insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes, usually develops in childhood or adolescence. There is a significantly higher mortality rate among children with type 1 diabetes compared with the general population of the similar age and sex.[1–3] In this group, the leading death mechanism was diabetic ketoacidosis (DKA), with cerebral edema accounting for two-thirds or more among all DKA deaths.[1,4–6] Also, DKA may be the first manifestation of type 1 diabetes in a minority of patients.

Fulminant type 1 diabetes (FTD1M) is a recently discovered subtype of type 1 diabetes which is classified not as autoimmune (type 1A) but as idiopathic (type 1B) diabetes. This disease is characterized by sudden onset and extremely rapid progression. The morbidity under 20 years of age is 8.7% in FTD1M patients of all ages according to Hanafusa's article.[7] Compared to type 1A diabetes, β cells are significantly reduced in fulminant type 1 diabetes. To date, most reports about this disease are from Japan. Although it is recognized that the death from FTD1M is inevitable if without timely treatment, but sudden and unexpected death from FTD1M is rarely reported and the death mechanism of this disease is not fully clarified. The cardiac arrest was thought to be one possible mechanism.[7] Here we described the unexpected death of a 15-year-old girl who was demonstrated to have FTD1M, DKA and lethal cerebral edema in the postmortem examination.

## 2. Case presentation

### 2.1. Case history

A 15-year-old Han Chinese girl went to see a doctor with a chief complaint of vomiting, fever and abdominal pain for about 24 h one day in the afternoon of early August in Fujian province. She was diagnosed with acute gastritis. She was prescribed injections of amikacin and alidine, the tablets of cidomycin, berberine and anisodamine. The symptoms were not relieved obviously. She still suffered from abdominal pain and weakness until she was found dead in bed at 4 am the next morning. Her relatives requested a forensic autopsy. Her family history was negative for diabetes mellitus and she had no relevant remarkable known medical history. And according to the supplemented memory from her relatives, the girl complained of fatigue, thirst and loss of appetite for some days, but without obvious weight loss. The relatives neglected it.

### 2.2. Autopsy findings

The body was preserved at room temperature (about 30 °C–26 °C) until a forensic autopsy was performed after 6 h since death.

* Corresponding author. Tel.: +86 18062128672; fax: +86 27 83692638.
*E-mail address:* hongmeidong1@hotmail.com (H. Dong).

http://dx.doi.org/10.1016/j.jflm.2014.05.001
1752-928X/

The body was that of a well-nourished girl. A punctiform abrasion was seen in the nasolabial groove. The needle puncture marks were seen on each lateral gluteal region. Multiple petechiae were seen in the epicardium. The heart weighed 190 g, and the brain weight was 1420 g. The cerebral gyri were flattened accompanied by shallower cortical sulci, and cerebellar tonsillar herniation was found. The liver weighed 1060 g and was yellow and greasy.

### 2.3. Histological, toxicological and biochemistry examination

Microscopically, slides of the brain showed extensive and severe edema. The granular layer of the cerebellum was remarkably swollen (Fig. 1). The hepatocytes and the epithelial cells of the renal proximal tubule were filled with vacuoles (Fig. 2), which were confirmed by Oil Red O stain to be lipid droplets, but PAS stain negative (Supplementary figure). The pancreatic islets were seriously damaged, and intact islets were hardly seen. Islet fibrosis was observed and the islet cells were notably reduced. The islets and stroma of the pancreas were infiltrated by dispersed lymphocytes. In contrast to the normal pancreas, insulin-positive cells were hardly detected by immunohistochemistry (Fig. 3). 190 insulin-positive islets were seen in fifty 10 × 10 visual fields for control pancreas, but no insulin-positive islets were seen in the reported case in the same fields. Other organs were unremarkable on gross or microscopic examination.

The heart blood and the vitreous fluid were collected at autopsy and sent to the lab for biochemistry analysis after autopsy. Then the blood sample and the vitreous fluid were centrifuged. The mild hemolysis was observed. The plasma and the supernatant of vitreous fluid were stored at −20 °C. The toxicology analysis revealed no positive findings. The traces of the prescribed drugs were present. The levels of the glucose and β-hydroxybutyrate were tested after 1 week of storage. The blood plasma glucose and β-hydroxybutyrate (the major component of the ketone bodies) were 12.4 mmol/L (ref: <6.1 mmol/L) and 6.3 mmol/L (ref: <0.3 mmol/L) respectively. The levels of glucose and β-hydroxybutyrate in the vitreous fluid were 14.2 mmol/L and 7.8 mmol/L. Since FT1DM was suspected highly, the other relevant biochemistry analysis was performed about 1.5 years after storage at −20 °C. Plasma HbA1c was 5.0% and C-protein was 0.05 nmol/L. The Abs of GAD and ICA were negative. Plasma amylase was 312 U/L (ref: 18–72 U/L).

## 3. Discussion

FTD1M was termed in 2000. The clinical diagnosis criteria for FTD1M were already well-established[7,8]: 1) development of ketosis within about one week after the onset of diabetic symptoms (average 4.4 days), 2) high blood glucose and near normal HbA1c (blood glucose more than 16.0 mmol/l and HbA1c less than 8.5% on the first examination), 3) virtually no C-peptide secretion (urinary C-peptide less than 10 μg/day or fasting serum <0.10 nmol/l). Except these indispensable features, the other clinical features are often seen: 1) absence of islet-related autoantibodies, such as ICA, GADAb, IAA, or IA-2Ab, 2) elevated serum pancreatic enzyme levels, 3) flue-like or gastrointestinal prodromal symptoms, 4) frequently pregnancy related. At postmortem, diagnosis of FTD1M is difficult because the disease is abrupt onset and the typical symptoms of diabetes are not obvious, moreover, the glucose and ketone levels of the blood and vitreous fluids were affected by postmortem changes and have remained undetected at routine postmortem examinations. In the case reported, the clinical manifestation of abdominal pain, nausea and vomiting is easily misdiagnosed as acute gastritis or acute pancreatitis if without the blood biochemistry. However, the acute pancreatitis was not being considered because the absence of neutrophils infiltration, necrosis of pancreas parenchyma and fat tissue, and hemorrhage as well in spite of elevated pancreatic enzyme levels. Severe islet destruction and insulitis were observed in the case, almost no remaining insulin-positive β cells could be seen by the histology and immunohistochemistry. Therefore, FTD1M was highly suspected combined with the clinical symptoms of the deceased.

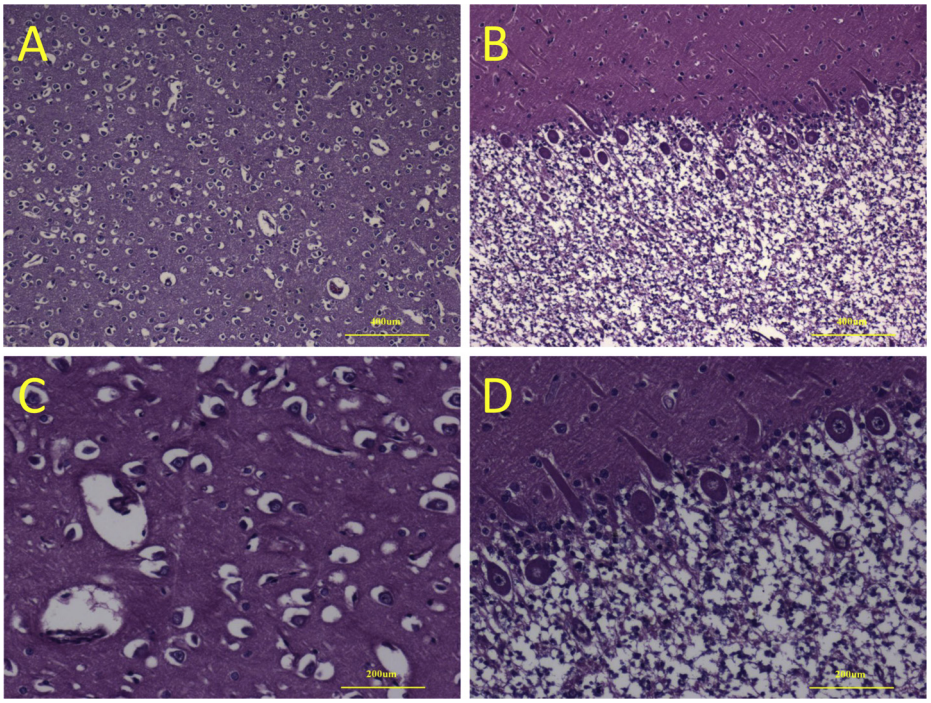


**Fig. 1.** Severe edema in the brain. A: perivascular, pericellular and interstitial edema in cerebrum. B: remarkable edema in the granule layer of cerebellum. C and D were the higher magnification of A and B. HE stain. Bars represent 400 μm in A and B, 200 μm in C and D.

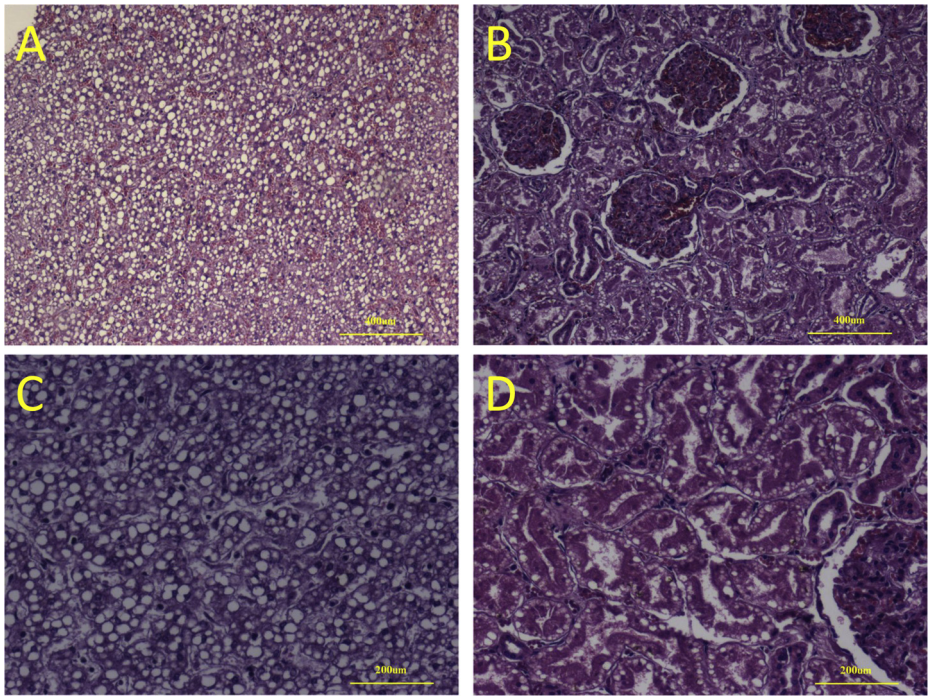


**Fig. 2.** Abundant lipid droplets in the cytoplasm of the hepatocytes and the epithelial cells of the renal proximal tubule. A: vacuole in the hepatocytes. B: vacuole in the epithelial cells of renal proximal tubule. C and D were the higher magnification of A and B. HE stain. Bars represent 400 μm in A and B, 200 μm in C and D.

As we know, the diagnosis of diabetes and DKA is usually based on biochemical analysis in clinical practice. The glucose levels in the blood and body fluids tend to decrease quickly after death due to postmortem glycolytic phenomena,[9] whereas HbA1c values are relatively stable within 72 h postmortem.[10] Vitreous humor glucose levels are less affected by postmortem changes but are lower than in blood. Coe suggested that antemortem vitreous glucose concentrations are 85% of the plasma glucose values.[11] According to the forensic literature, DKA could be determined to be the cause of death when vitreous glucose concentrations were more than 10 mmol/l (104 mg/dl) and femoral (or cardiac) blood b-HB levels higher than 2.5 mmol/l (26 mg/dl), as well as when other causes of death were excluded based on all postmortem examinations.[12–14] To confirm the diagnostic value of blood glucose and ketone, we analyzed the blood glucose and ketone levels from three deceased (normal individuals), the result showed normal. In contrast, the values of glucose and ketone in the above case reported were highly elevated. Moreover, the values were higher in vitreous humor than in blood in the case, which also indicated that the glucose and ketone of vitreous humor were more stable and reliable at postmortem. Therefore, considering postmortem changes, we thought that ketoacidosis associated with a rapid onset of hyperglycemia occurred before death. Together with the other biochemistry indicator, such as HbA1C, C-peptide, plasma amylase, and islet-related autoantibodies, the cause of death was identified as FTD1M.

An abundance of literature indicated that cerebral edema is the most common cause of DKA-induced mortality in young children with type 1 diabetes, but most of the cerebral edema was diagnosed by CT or MRI clinically rather than by postmortem histology. In the report, severe cerebral edema was discovered at postmortem. The pathology change of brain edema and fatty degeneration in the liver, hallmarks of Reye's syndrome, were referred in a case report of FT1DM,[15] both of which were observed in the current case. Although the mechanism of cerebral edema due to DKA remains to be clarified, the current case indicated that the 15-year-old girl was very likely to die from DKA-induced cerebral edema which was conformed to common type 1 diabetes.

The other interesting histological findings in the case were the hepatocytes and the epithelial cells of the renal proximal tubule were diffusely filled with lipid droplets. The diabetic vacuole of the renal tubular epithelial cells is usually regarded as an accumulation of glycogen (the Armanni-Ebstein change), but the vacuole was proved by histochemical stain to be fat and not glycogen in this case. It was controversial that the lipid deposition in renal tubular epithelial cells was termed as Armanni-Ebstein change.[12] Armanni-Ebstein lesions can also be seen in non-diabetic ketoacidosis resulting from alcoholism and other reasons.[16] Nielsen's study indicated that the lipid vacuolar lesions of the renal tubular epithelial cells were present in a diabetic coma but not in non-coma diabetics.[17] The diffuse hepatic steatosis, a non-specific finding in diabetes was also observed in the case. The lipid droplets in the hepatocytes and renal tubular epithelial cells enhanced our understanding about the metabolism in type 1 diabetes and its possible diagnostic value .[18–21] Although the histology finding in the kidney and liver might not be pathognomonic for diabetes or FTD1M, we recommend strongly that is helpful for postmortem diagnosis of diabetes.

Sudden unexpected death was one of the predominant causes of death in young individuals with diabetes according to Tu's research.[22] The most common cause of sudden death was attributed to "dead in bed" syndrome in type 1 diabetes of people under the age of 40. Thus, this case also needs to exclude the possibility of 'dead in bed' syndrome. Victims of this particular type of sudden death showed some characters in common: usually good health condition and being found dead in undisturbed bed the next morning. Hypoglycaemia, a hypoglycaemia-associated event or autonomic dysfunction is thought to be responsible for this kind of death. In these cases, the postmortem examination did not reveal any macroscopic, histological or toxicological evidences that could explain the cause of the sudden death. Although circumstances, such as the timing of death in the described case here coincided

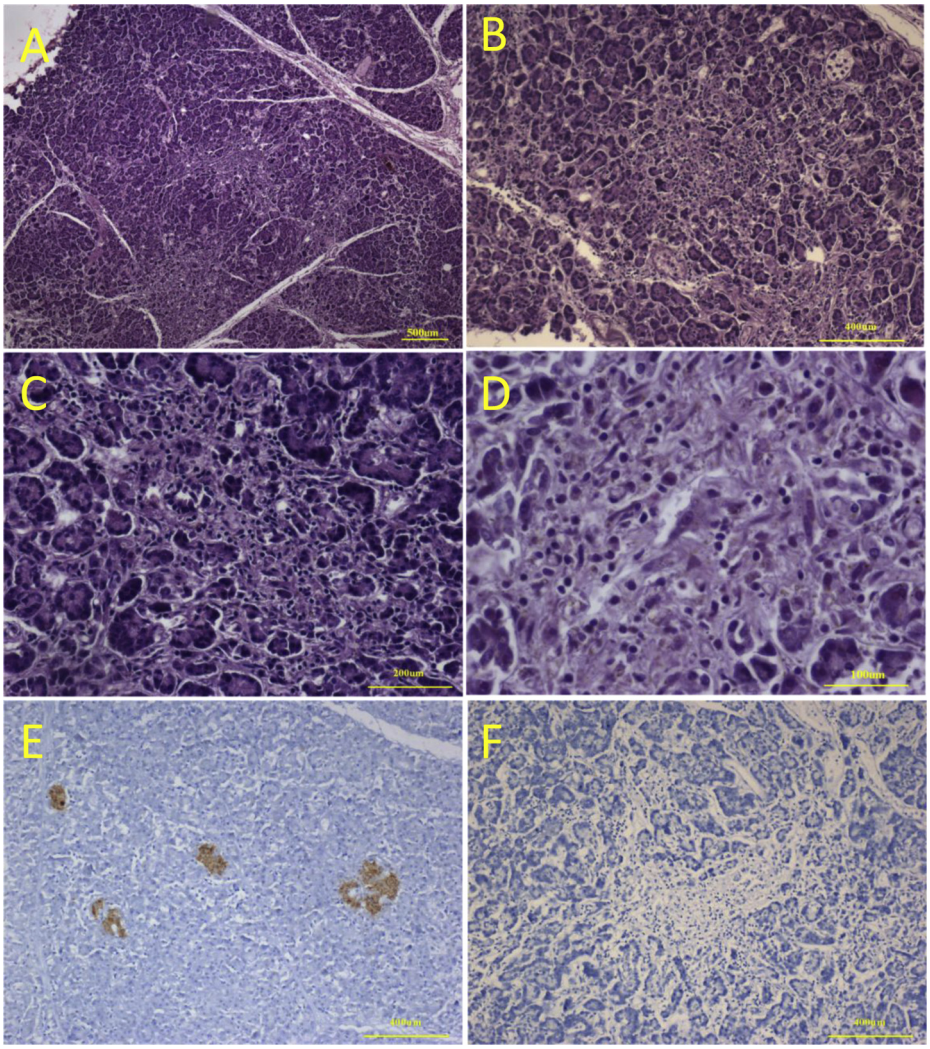


**Fig. 3.** The histology and immunohistochemistry of the pancreas. A, B, C and D: diffuse islet fibrosis, and lymphocytes infiltrated in islets and stroma of the pancreas. A, B, C and D were the different higher magnification. A: HE 40×; B: 100×; C: 200×; D: 400×. E,F: insulin expression in the islets by immunohistochemistry: insulin expression was positive in normal islets (E, control), and insulin was nearly negative in the islets of the reported case (F). Bar represents 500 μm in A, 400 μm in B, E and F, 200 μm in C, 100 μm in D.

with those in the 'dead in bed' syndrome, this case didn't meet the criteria of being well before death and a negative autopsy of the 'dead in bed' syndrome.

To the best of our knowledge, FTD1M presenting with sudden death was rare. There are only few similar clinico-pathological report were found, the preceding gastroenteritis-like symptoms, the histology finding including pancreas, liver, and kidney were very similar to the current case.[23,24] The case demonstrates that the specific histology findings in pancreas, insulin immunohistochemistry in combination with the fatty vacuoles in the hepatocytes and the epithelial cells of the renal proximal tubule may be a useful pathological diagnostic way for FTD1M as the cause of death at postmortem. Furthermore, analysis of this case also emphasizes the importance of a careful medical care and an evenly distributed high-level medical system, in order that the patients at risk can be discovered as early as possible.

*Ethical approval*

None declared.

*Funding*

No funding.

*Conflict of interest*

We declared that no any conflict of interest existed in this submitted manuscript.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jflm.2014.05.001.

## References

1. Edge JA, Ford-Adams ME, Dunger DB. Causes of death in children with insulin dependent diabetes 1990–96. *Arch Dis Child* 1999;**81**:318–23.
2. Dahlquist G, Kallen B. Mortality in childhood-onset type 1 diabetes: a population-based study. *Diabetes Care* 2005;**28**:2384–7.
3. Bruno G, Cerutti F, Merletti F, Novelli G, Panero F, Zucco C, et al. Short-term mortality risk in children and young adults with type 1 diabetes: the population-based Registry of the Province of Turin, Italy. *Nutr Metab Cardiovasc Dis* 2009;**19**:340–4.
4. Edge JA, Jakes RW, Roy Y, Hawkins M, Winter D, Ford-Adams ME, et al. The UK case-control study of cerebral oedema complicating diabetic ketoacidosis in children. *Diabetologia* 2006;**49**:2002–9.
5. Edge JA, Hawkins MM, Winter DL, Dunger DB. The risk and outcome of cerebral oedema developing during diabetic ketoacidosis. *Arch Dis Child* 2001;**85**:16–22.

6. Shastry RM, Bhatia V. Cerebral edema in diabetic ketoacidosis. *Indian Pediatr* 2006;**43**:701–8.
7. Hanafusa T, Imagawa A. Fulminant type 1 diabetes: a novel clinical entity requiring special attention by all medical practitioners. *Nat Clin Pract Endocrinol Metab* 2007;**3**:36–45.
8. Imagawa A, Hanafusa T. Pathogenesis of fulminant type 1 diabetes. *Rev Diabet Stud* 2006;**3**:169.
9. Gormsen H, Lund A. The diagnostic value of postmortem blood glucose determinations in cases of diabetes mellitus. *Forensic Sci Int* 1985;**28**:103–7.
10. Uemura K, Shintani-Ishida K, Saka K, Nakajima M, Ikegaya H, Kikuchi Y, et al. Biochemical blood markers and sampling sites in forensic autopsy. *J Forensic Legal Med* 2008;**15**:312–7.
11. Coe J. Postmortem chemistries on human vitreous humor. *Am J Clin Pathol* 1969;**51**:741.
12. Iten P, Meier M. Beta-hydroxybutyric acid—an indicator for an alcoholic ketoacidosis as cause of death in deceased alcohol abusers. *J Forensic Sci* 2000;**45**:624–32.
13. Palmiere C, Sporkert F, Vaucher P, Werner D, Bardy D, Rey F, et al. Is the formula of Traub still up to date in antemortem blood glucose level estimation? *Int J Legal Med* 2012;**126**:407–13.
14. Zilg B, Alkass K, Berg S, Druid H. Postmortem identification of hyperglycemia. *Forensic Sci Int* 2009;**185**:89–95.
15. Hasegawa G, Ohashi R, Naito M, Takagi A. An autopsy case of fulminant type 1 diabetes accompanying Reye's syndrome. *Endocr J* 2005;**52**:159.
16. Milroy C, Parai J. Armanni-Ebstein lesion, ketoacidosis and starvation in a child. *Forensic Sci Med Pat* 2011;**7**:213–6.
17. Nielsen H, Thomsen JL, Kristensen IB, Ottosen PD. Accumulation of triglycerides in the proximal tubule of the kidney in diabetic coma. *Pathology* 2003;**35**:305–10.
18. Thomsen JL, Hansen TP. Lipids in the proximal tubules of the kidney in diabetic coma. *Am J Forensic Med Pathol* 2000;**21**:416–8.
19. Rozin L, Perper JA, Jaffe R, Drash A. Sudden unexpected death in childhood due to unsuspected diabetes mellitus. *Am J Forensic Med Pathol* 1994;**15**:251–6.
20. Kodikara S, Paranitharan P, Pollanen MS. The role of the Armanni-Ebstein lesion, hepatic steatosis, biochemical analysis and second generation antipsychotic drugs in fatal diabetic ketoacidosis. *J Forensic Legal Med* 2012;**20**:108–11.
21. Zhou C, Yool AJ, Nolan J, Byard RW. Armanni-Ebstein lesions: a need for clarification. *J Forensic Sci* 2013;**58**:S94–8.
22. Tu E, Twigg SM, Duflou J, Semsarian C. Causes of death in young Australians with type 1 diabetes: a review of coronial postmortem examinations. *Med J Aust* 2008;**188**:699.
23. Furukawa S, Yamamoto Y, Nakagawa T, Sakaguchi I, Nishi K. An autopsy case of fulminant Type 1 diabetes mellitus with lymphocytes infiltration of the thyroid gland and the pancreas. *Anil Aggrawal's Internet J Forensic Med Toxicol* 2011;**12**:12.
24. Mizutani T, Yoshimoto T, Kaneko R, Ishii A. Diagnosis of fulminant type 1 diabetes mellitus in an autopsy case with postmortem changes. *Leg Med* 2011;**13**:250–3.